

PATENT COOPERATION TREATY

PCT

REC'D 2 AUG 1999

INTERNATIONAL PRELIMINARY EXAMINATION REPORT PCT

(PCT Article 36 and Rule 70)



Applicant's or agent's file reference A018PCT	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/US98/07587	International filing date (day/month/year) 16/04/1998	Priority date (day/month/year) 18/04/1997
International Patent Classification (IPC) or national classification and IPC C12N15/62		
Applicant BIOGEN, INC. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 6 sheets, including this cover sheet.
 - ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☒ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☒ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☒ Certain observations on the international application

Date of submission of the demand 18/11/1998	Date of completion of this report 27.07.99
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. (+49-89) 2399-0 Tx: 523656 epmu d Fax: (+49-89) 2399-4465	Authorized officer Fotaki, M Telephone No. (+49-89) 2399 8709 

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/US98/07587

I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1-61 as originally filed

Claims, No.:

1-21 as originally filed

2. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

II. Priority

1. ☐ This report has been established as if no priority had been claimed due to the failure to furnish within the prescribed time limit the requested:

- ☐ copy of the earlier application whose priority has been claimed.
☐ translation of the earlier application whose priority has been claimed.

2. ☐ This report has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid.

Thus for the purposes of this report, the international filing date indicated above is considered to be the relevant date.

**INTERNATIONAL PRELIMINARY
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3. Additional observations, if necessary:

see separate sheet

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims 4, 14-21
	No:	Claims 1-3, 5-13
Inventive step (IS)	Yes:	Claims none
	No:	Claims 1-21
Industrial applicability (IA)	Yes:	Claims 1-13
	No:	Claims 14-21 (reserved opinion)

2. Citations and explanations

see separate sheet

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/US98/07587

II. PRIORITY

- 1) This first preliminary written opinion has been established considering the priority date 18.04.97 as a valid date. The attention of the Applicant is drawn to the fact that document:

US 5693607 A published 02.12.97

not cited in the international search report, may become relevant after consideration of the priority document which is unavailable at present.

V. REASONED STATEMENT UNDER ARTICLE 35(2)

- 2) The present application relates to fusion proteins comprising part of the receptor for the transforming growth factor- β (TGF- β) and part of an immunoglobulin (IgG). The generated fusion protein comprises the extracellular domain of the type II receptor of TGF- β (TGF- β RII) and the constant region (Fc) of IgG. Said fusion proteins are intended to inhibit the binding of TGF- β to its receptor, thus, having an application as TGF- β antagonists in fibroproliferative disorders such as diabetic nephropathy and human mesangial proliferative glomerulonephritis.

- 3) The subject-matter of **Claim 1** is not novel as required by Article 33(2) PCT. Said claim relates to a fusion protein comprising a part of a TGF- β receptor, said fusion protein has the technical effect of inhibiting the binding of TGF- β to TGF- β receptor.

Document D1: OKADOME T ET AL: J BIOL CHEM, DEC 9 1994, 269 (49) P30753-6, discloses a fusion protein, called T β R-2.1, comprising the extracellular domain of TGF- β receptor II and the intracellular domain of TGF- β receptor I. Said fusion protein is capable of binding the ligand TGF- β (p. 30754) and thus, it is capable of inhibiting the binding of said ligand to its native receptor, the TGF- β receptor. Hence the subject-matter of **Claim 1** is not novel. Similarly, the subject-matter of **Claims 2, 5, 6, 8-13** is not novel either.

- 4) The subject-matter of **Claim 3** relates to a fusion protein comprising the extracellular fragment of TGF- β receptor type II and the constant region of an IgG.

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The document D2: WO 94 09815, published on 11.05.94 is not cited in the international search report.

Document D2 discloses a fusion of said extracellular fragment of TGF- β receptor type II with human immunoglobulin (p. 20). Thus, the subject-matter of **Claims 3 and 7** is not novel as required by Article 33(2) PCT.

- 5) The subject-matter of **Claim 4** relates to a fusion protein comprising the extracellular fragment of TGF- β receptor type II and the constant region of IgG characterized by the amino acid sequence presented as SEQ ID 8 or 9.

Document D2 discloses the provision of a fusion protein comprising the extracellular fragment of the type II receptor for TGF- β and IgG as an antagonist for TGF- β .

The problem to be solved appears to be the provision of said fusion protein characterized by a defined amino acid sequence.

Document D3: WO 94 17828, 18 August 1994, discloses a fusion protein comprising VCAM and the human IgG1 heavy chain constant region characterized by the amino acid sequence SEQ ID NO 9 (p. 35). Thus, methods for the provision of fusion proteins comprising the IgG constant region and defined sequence encoding the same are available to the skilled person should he be faced with the above mentioned technical problem. Hence, the subject-matter of **Claim 4** does not involve an inventive step as required by Article 33(3) PCT.

- 6) The subject-matter of **Claim 14** relates to a method for lowering the levels of TGF- β in an individual in need thereof which comprises the use of an TGF- β antagonist which is a fusion protein comprising the rabbit or human extracellular fragment of TGF- β receptor type II and the constant domain of IgG characterized by the SEQ ID NOS 8 or 9.

Document D2 discloses the use of the extracellular fragment of TGF- β receptor type II in treating medical conditions associated with TGF- β excess (p. 7, 10). A disclosed mode of administration of said fragment is a fusion of said fragment with

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/US98/07587

human immunoglobulin (p. 20).

The problem to be solved is the provision of a method of treating a medical condition associated with TGF- β excess wherein the antagonist of TGF- β is a fusion protein with defined amino acid sequence.

Document D3 discloses methods of construction fusion protein comprising IgG constant region as well as defined sequences thereof. Thus, the person skilled in the art seeking to solve the above mentioned technical problem will follow the teachings of document D2 in providing an antagonist of TGF- β in combination with teachings of document D3 of how to construct said antagonist. Thus, the subject-matter of **Claims 14-21** do not involve an inventive step as required by Article 33(3) PCT.

- 7) For the assessment of the present **Claims 14-21** as far as they are directed to a method of treatment of the human or animal body or to a diagnostic method practised on the human or animal body, no unified criteria exist in the PCT, on the question whether they are industrially applicable. The patentability can be dependent upon the formulation of the claims.

VI. CERTAIN DOCUMENTS CITED

- 8) The following document is cited under Rule 70.10 PCT
US 5 693 607 published 02.12.97 and filed on 22.12.94

VIII. CERTAIN OBSERVATIONS ON THE INTERNATIONAL APPLICATION

- 9) The subject-matter of **Claim 9** is not clear as required by Rule 6 PCT because the SEQ ID NOS 10 or 12 do not encode an isolated polynucleotide according to **Claim 8**.
- 10) **Claims 1, 2, 5, 6, 8-10, 13-17** do not meet the requirements of Rule 6 for clarity. The term TGF should appear in full name, at least once, with the abbreviated form next to it, in brackets.

PATENT COOPERATION TREATY

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

United States Patent and Trademark
Office
(Box PCT)
Crystal Plaza 2
Washington, DC 20231
ÉTATS-UNIS D'AMÉRIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 11 December 1998 (11.12.98)	
International application No. PCT/US98/07587	Applicant's or agent's file reference A018PCT
International filing date (day/month/year) 16 April 1998 (16.04.98)	Priority date (day/month/year) 18 April 1997 (18.04.97)
Applicant GOTWALS, Philip et al	

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International Preliminary Examining Authority on:

18 November 1998 (18.11.98)

☐ in a notice effecting later election filed with the International Bureau on:2. The election ☒ was☐ was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.: (41-22) 740.14.35	Authorized officer E. Huchon Telephone No.: (41-22) 338.83.38
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TENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

<p>To:</p> <p>BIOGEN, Inc. Attn. WARREN, A. 14 Cambridge Center Cambridge, Ma 02142 UNITED STATES OF AMERICA</p>	<p>BIOGEN, INC.-IP DEPT.</p> <div style="border: 1px solid black; padding: 5px; margin: 5px auto; width: 80px;"> <p>PCT 8 1998</p> </div> <p>REFERRED TO NOTED BY _____ <i>WAL</i></p>	<p>NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT OR THE DECLARATION</p> <p style="text-align: right;">(PCT Rule 44.1)</p>
		<p>Date of mailing (day/month/year) 01/10/1998</p>
<p>Applicant's or agent's file reference A018PCT</p>		<p>FOR FURTHER ACTION See paragraphs 1 and 4 below</p>
<p>International application No. PCT/US 98/ 07587</p>		<p>International filing date (day/month/year) 16/04/1998</p>
<p>Applicant</p> <p>BIOGEN, INC. et al.</p>		

1. ☒ The applicant is hereby notified that the International Search Report has been established and is transmitted herewith.

Filing of amendments and statement under Article 19

The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

Where? Directly to the International Bureau of WIPO
 34, chemin des Colombettes
 1211 Geneva 20, Switzerland
 Facsimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. ☐ The applicant is hereby notified that no International Search Report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. ☐ **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicants's request to forward the texts of both the protest and the decision thereon to the designated Offices.

☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Further action(s):** The applicant is reminded of the following:

Shortly after **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90bis.1 and 90bis.3, respectively, before the completion of the technical preparations for international publication.

Within **19 months** from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within **20 months** from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

<p>Name and mailing address of the International Searching Authority</p> <p>European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016</p>	<p>Authorized officer</p> <p>Barbara Klaver Entered Computer <i>ju</i></p>
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NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When?

Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How?

Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

NOTES TO FORM PCT/ISA/220 (continued)

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

- (i) the claim is unchanged;
- (ii) the claim is cancelled;
- (iii) the claim is new;
- (iv) the claim replaces one or more claims as filed;
- (v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."
2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."
3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."
4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international application is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.2(a), first sentence).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, where upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

TENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

BIOGEN, INC-IP DEPT.

OCT 8 1998

REFERRED TO
NOTED BY

Applicant's or agent's file reference A018PCT	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. PCT/US 98/ 07587	International filing date (day/month/year) 16/04/1998	(Earliest) Priority Date (day/month/year) 18/04/1997
Applicant BIOGEN, INC. et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 4 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. ☒ Certain claims were found unsearchable (see Box I).

2. ☐ Unity of invention is lacking (see Box II).

3. ☒ The international application contains disclosure of a nucleotide and/or amino acid sequence listing and the international search was carried out on the basis of the sequence listing

☒ filed with the international application.

☐ furnished by the applicant separately from the international application,

☐ but not accompanied by a statement to the effect that it did not include matter going beyond the disclosure in the international application as filed.

☐ Transcribed by this Authority

4. With regard to the title, ☐ the text is approved as submitted by the applicant

☒ the text has been established by this Authority to read as follows:

TYPE II TGF-BETA RECEPTOR / IMMUNOGLOBULIN CONSTANT REGION FUSION PROTEINS

5. With regard to the abstract,

☒ the text is approved as submitted by the applicant

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this International Search Report, submit comments to this Authority.

6. The figure of the drawings to be published with the abstract is:

Figure No. — ☐ as suggested by the applicant.

☐ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

☐ None of the figures.

INTERNATIONAL SEARCH REPORT

national application No.

PCT/US 98/07587

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claim 14-21 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Int'l Application No

PCT/US 98/07587

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C12N15/62 C07K14/71 A61K38/17

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C12N C07K A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	OKADOME T ET AL: "Distinct roles of the intracellular domains of transforming growth factor-beta type I and type II receptors in signal transduction." J BIOL CHEM, DEC 9 1994, 269 (49) P30753-6, XP002077575 UNITED STATES	1,2,5,6, 8-13
Y	see the whole document	3,4,7, 14-21
Y	WO 94 17828 A (BIOGEN INC ;BURKLY LINDA C (US)) 18 August 1994 see claims 1-17; figure 8; example 5 -/--	3,4,7, 14-21

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

° Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

22 September 1998

Date of mailing of the international search report

01/10/1998

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Nauche, S

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 98/07587

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	ANDERS RA ET AL: "Chimeric granulocyte/macrophage colony-stimulating factor/transforming growth factor-beta (TGF-beta) receptors define a model system for investigating the role of homomeric and heteromeric receptors in TGF-beta signaling." J BIOL CHEM, SEP 6 1996, 271 (36) P21758-66, XP002077576 UNITED STATES see the whole document ---	1-21
A	WO 96 26964 A (PROTEIN DESIGN LABS INC ; IOWA IMMUNOTHERAPY INVESTIGATO (US)) 6 September 1996 see the whole document -----	3,4,7, 14-21

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 98/07587

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9417828 A	18-08-1994	AT 161730 T	15-01-1998
		AU 687790 B	05-03-1998
		AU 6237994 A	29-08-1994
		AU 6984698 A	23-07-1998
		CA 2155303 A	18-08-1994
		DE 69407758 D	12-02-1998
		DE 69407758 T	27-08-1998
		EP 0682529 A	22-11-1995
		ES 2114183 T	16-05-1998
		JP 8508719 T	17-09-1996
		NZ 262615 A	27-02-1996
WO 9626964 A	06-09-1996	AU 5090496 A	18-09-1996
		CA 2212750 A	06-09-1996
		EP 0812333 A	17-12-1997

PATENT COOPERATION TREATY
PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference A018PCT	FOR FURTHER ACTION <small>see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.</small>	
International application No. PCT/US 98/ 07587	International filing date (day/month/year) 16/04/1998	(Earliest) Priority Date (day/month/year) 18/04/1997
Applicant BIOGEN, INC. et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 4 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. ☒ **Certain claims were found unsearchable** (see Box I).

2. ☐ **Unity of invention is lacking** (see Box II).

3. ☒ The international application contains disclosure of a **nucleotide and/or amino acid sequence listing** and the international search was carried out on the basis of the sequence listing

☒ filed with the international application.

☐ furnished by the applicant separately from the international application.

☐ but not accompanied by a statement to the effect that it did not include matter going beyond the disclosure in the international application as filed.

☐ Transcribed by this Authority

4. With regard to the **title**, ☐ the text is approved as submitted by the applicant

☒ the text has been established by this Authority to read as follows:

TYPE II TGF-BETA RECEPTOR / IMMUNOGLOBULIN CONSTANT REGION FUSION PROTEINS

5. With regard to the **abstract**,

☒ the text is approved as submitted by the applicant

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this International Search Report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is:

Figure No. — ☐ as suggested by the applicant.

☐ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

☐ None of the figures.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 98/ 07587

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claim 14-21 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

National Application No

PCT/US 98/07587

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C12N15/62 C07K14/71 A61K38/17

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C12N C07K A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	OKADOME T ET AL: "Distinct roles of the intracellular domains of transforming growth factor-beta type I and type II receptors in signal transduction." J BIOL CHEM, DEC 9 1994, 269 (49) P30753-6, XP002077575 UNITED STATES	1,2,5,6, 8-13
Y	see the whole document	3,4,7, 14-21
Y	WO 94 17828 A (BIOGEN INC ;BURKLY LINDA C (US)) 18 August 1994 see claims 1-17; figure 8; example 5 -/--	3,4,7, 14-21

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

22 September 1998

Date of mailing of the international search report

01/10/1998

Name and mailing address of the ISA

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Authorized officer

Nauche, S

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 98/07587

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>ANDERS RA ET AL: "Chimeric granulocyte/macrophage colony-stimulating factor/transforming growth factor-beta (TGF-beta) receptors define a model system for investigating the role of homomeric and heteromeric receptors in TGF-beta signaling." J BIOL CHEM, SEP 6 1996, 271 (36) P21758-66, XP002077576 UNITED STATES see the whole document ----</p>	1-21
A	<p>WO 96 26964 A (PROTEIN DESIGN LABS INC ;IOWA IMMUNOTHERAPY INVESTIGATO (US)) 6 September 1996 see the whole document -----</p>	3,4,7, 14-21

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 98/07587

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9417828 A	18-08-1994	AT 161730 T	15-01-1998
		AU 687790 B	05-03-1998
		AU 6237994 A	29-08-1994
		AU 6984698 A	23-07-1998
		CA 2155303 A	18-08-1994
		DE 69407758 D	12-02-1998
		DE 69407758 T	27-08-1998
		EP 0682529 A	22-11-1995
		ES 2114183 T	16-05-1998
		JP 8508719 T	17-09-1996
		NZ 262615 A	27-02-1996
WO 9626964 A	06-09-1996	AU 5090496 A	18-09-1996
		CA 2212750 A	06-09-1996
		EP 0812333 A	17-12-1997

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 98/ 07587

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claim 14-21 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.